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STENTS COMPRISING SGC ACTIVATORS

Coronary diseases caused by arteriosclerosis are treated inter alia by the currently usual method of percutaneous transluminal coronary angioplasty (PTCA). For this purpose, a balloon catheter is introduced into the narrowed or blocked artery, which is then widened through expansion of the balloon, and the blood flow is thus restored. A problem in this connection, occurring in about 30% of cases, is the acute reocclusion, occurring immediately after the PTCA (acute restenosis), or the later, subacute (restenosis) reocclusion, of the blood vessel.

The risk of acute restenosis can be reduced by administration of platelet aggregation inhibitors. An additional possibility is mechanical support of the coronary wall by a normally cylindrical and expandable mesh (stent) which is introduced into the diseased vessel and unfolds at the site of the stenosis in order to open the narrowed place and keep it open by supporting the blood vessel wall. Although it is possible by this method to reduce the risk of restenosis slightly, at present there is still no convincing therapy available for subacute restenosis.

A newer possibility for the treatment of restenosis is local administration of the active ingredient by means of a stent which releases the active ingredient. The combination of active ingredient and stent makes medical treatment and mechanical stabilization possible in one application.

Thus, the combination of stents with active ingredients makes it possible for the local concentration of active ingredient to be high without unwanted systemic side effects (e.g. hemorrhages or stroke) occurring.

It is possible for this purpose to coat stents with active ingredient-containing coating materials. The active ingredient release takes place by diffusion from the coating or through breakdown of the coating when biodegradable coating systems are used.

Another possibility which has already been described is the preparation of small cavities or micropores in the stent surface, into which the active ingredient or else active ingredient-containing polymeric coating systems are embedded (see, for example, EP-A 0 950 386). An active ingredient-free coating can subsequently be applied. Release takes place by diffusion or degradation or by a combination of the two processes.

In addition, active ingredient-containing stents can be produced by melt embedding the active ingredient in a polymeric carrier, e.g. with the aid of injection molding processes. Release of the active ingredient from these stents usually takes place through diffusion.

It has now been found, surprisingly, that sGC activators are particularly suitable as active ingredients for this type of treatment, in particular for the treatment and/or prophylaxis of restenoses and/or thromboses after PTCA.

sGC activators are compounds which stimulate soluble guanylate cyclase by a mechanism which proceeds independently of the presence of the heme group of the enzyme (Brit. J. of Pharmacology, **136** (2002) 637-640 and 773-783).

Substances of this type are disclosed for example in WO 01/19776, WO 01/19355, WO 01/19780 and WO 01/19778. The contents of these documents, in particular the compounds mentioned generally therein and especially those mentioned specifically therein form an express part of the description of the present invention.

The present invention therefore describes the use of one or more sGC activators, where appropriate in combination with one or more other active ingredients, for producing a release system comprising medicinal substance(s), in particular a stent comprising medicinal substance(s).

In addition, the present invention describes a release system, in particular a stent,

which comprises one or more sGC activators, where appropriate in combination with one or more other active ingredients, and which makes targeted release of one or more sGC activators, and of other active ingredients present where appropriate, at the site of action (drug targeting) possible, and are thus suitable for the prophylaxis and/or treatment of restenoses and/or thromboses, in particular after PTCA.

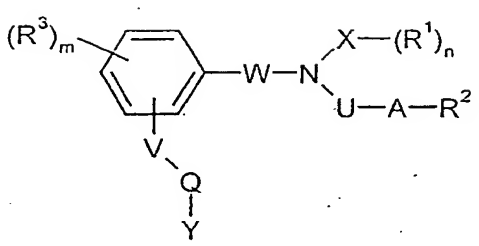
The present invention likewise describes a method for the treatment and/or prophylaxis of restenoses and/or thromboses by using one or more sGC activators in combination with a stent. In this use it is possible for one such compound to be employed either systemically or, preferably, in the form of a stent comprising one such compound.

Whereas it is not possible with the active ingredients and stents currently available to achieve an adequate success of therapy in all cases, the novel combination of sGC activators with a stent makes more effective treatment and/or prophylaxis of restenoses and/or thromboses possible. Local administration of sGC activators in combination with a stent makes it possible to reduce the dose of the medicinal substance necessary to prevent restenoses and/or thromboses. It is thus possible to minimize undeplored systemic effects. At the same time, the local concentration can be increased and thus the efficacy enhanced.

It is moreover possible, in addition to the administration according to the invention, for a local and/or systemic administration of other active ingredients suitable for the treatment and/or prophylaxis of restenoses and/or thromboses to take place, such as, for example and preferably, abciximab, eptifibatide, tirofiban, acetylsalicylic acid, ticlopidine or clopidogrel. Additional systemic treatment with sGC activators is preferred, especially by oral administration.

The present invention thus relates to stents comprising sGC activators.

Preference is given to stents comprising compounds of the formula (I)



(I),

in which

V is O,

Q is CH_2,

Y is phenyl which is substituted by a radical which is selected from the group consisting of 2-phenylethyl, cyclohexyl, 4-chlorophenyl, 4-methoxyphenyl, 4-trifluoromethylphenyl, 4-cyanophenyl, 4-chlorophenoxy, 4-methoxyphenoxy, 4-trifluoromethylphenoxy, 4-cyanophenoxy, 4-methylphenyl,

R^3 is hydrogen or fluorine,

m is an integer from 1 to 2,

W is $-CH_2CH_2-$,

U is $-CH_2-$,

A is phenyl,

R^2 is COOH, where R_2 is disposed in the 4-position relative to the radical U,

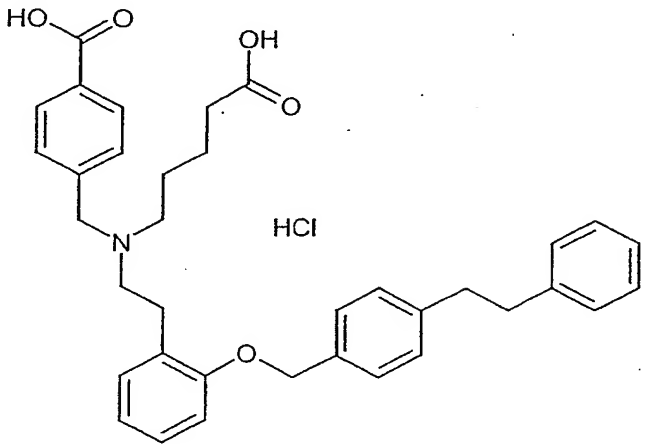
X is $(CH_2)_4$,

R^1 is COOH,

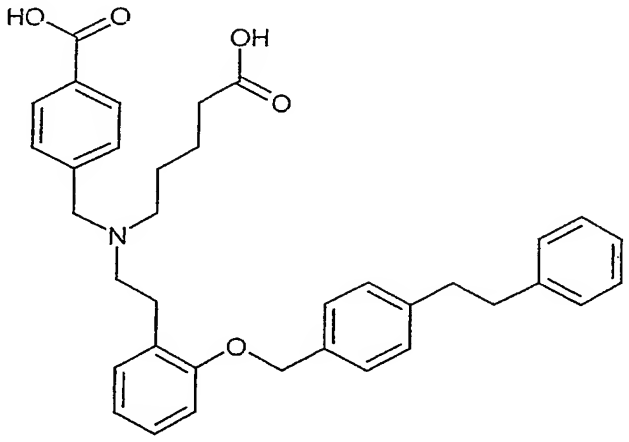
and the salts, hydrates and hydrates of the salts thereof.

Particular preference is given to stents comprising compounds of the formula (I) having the following structures:

4-[((4Carboxybutyl)-{2-[(4-phenethylbenzyl)oxy]phenethyl}amino)methyl]benzoic acid hydrochloride



4-[((4Carboxybutyl)-{2-[(4-phenethylbenzyl)oxy]phenethyl}amino)methyl]benzoic acid



The preparation of the compounds of the formula (I) is described in WO 01/19780. The two particularly preferred, explicitly mentioned compounds are Examples 8 and 8a described on pages 103 to 104 of WO 01/19780.

Release systems comprising the compounds of the invention of the formula (I) are produced by using conventional stents where the basic body of the stent consists either of metals or undegradable plastics such as, for example and preferably, polyethylene, polypropylene, polycarbonate, polyurethane and/or polytetrafluoroethylene (PTFE). In addition, stents with various designs of the metal mesh, which make various surfaces and folding principles possible and as described, for example, in WO 01/037761, WO 01/037892, are used as basic body of the stent.

These stents are coated and/or filled with the compounds of the formula (I). An alternative possibility in the case of nonmetallic stents is to incorporate compounds of the formula (I) directly into the material used to produce the stents.

Carrier materials are mixed with the compounds of the formula (I) for the coating or filling. Carrier materials used for this purpose are preferably polymeric carriers, in particular biocompatible, non-biodegradable polymers or polymer mixtures, such as, for example and preferably, polyacrylates and copolymers thereof such as, for example and preferably, poly(hydroxyethyl)methylmethacrylates; polyvinylpyrrolidones; cellulose esters and ethers; fluorinated polymers such as, for example and preferably, PTFE; polyvinyl acetates and copolymers thereof; crosslinked and uncrosslinked polyurethanes, polyethers or polyesters; polycarbonates; polydimethylsiloxanes. As an alternative, biocompatible, biodegradable polymers or polymer mixtures such as, for example and preferably, polymers or copolymers of lactide and glycolide, or of caprolactone and glycolide; other polyesters; polyorthoesters; polyanhydrides; polyamino acids; polysaccharides; polyiminocarbonates; polyphosphazenes and poly(ether-ester) copolymers are also used as polymeric carriers.

Also suitable as polymeric carriers are mixtures of biodegradable and/or non-biodegradable polymers. The rate of release of the active ingredient is adjusted optimally through these mixtures.

Coated or filled stents are produced by dissolving the mixtures of compounds of the formula (I) and carrier, preferably in suitable solvents. These solutions are then applied to the stent by various techniques such as, for example, spraying, dipping or brush-coating. Subsequent or simultaneous removal of the solvent results in the stent provided with active ingredient-containing coating. An alternative possibility is also for mixtures of compounds of the formula (I) and carrier to be melted and applied by the same application methods.

The stents are preferably pretreated in order to enlarge the outer and/or inner surface area of the stent. This increases the loading potential and larger amounts of coating (active ingredient/polymer) can be applied. Various etching techniques, but also treatments with ionized radiation, for example, are used for the pretreatment of the stents. It is likewise possible to produce micropores or cavities in the stents with the aid of various techniques.

The active ingredient contents of the stents coated or filled with compounds of the formula (I) are usually from 0.001% by weight to 50% by weight, preferably from 0.01% by weight to 30% by weight, particularly preferably 0.1% by weight to 15% by weight.

In the case of nonmetallic stents, the compounds of the formula (I) can also be incorporated directly for example as melt embedding in the basic body of the stent. In these cases, active ingredient-containing polymeric carrier materials are processed by conventional methods, for example by injection molding processes, to give the final active ingredient-containing form. In these cases, the active ingredient is usually released by diffusion.

The active ingredient contents of stents with embedded compounds of the formula (I) are usually from 0.001% by weight to 70% by weight, preferably from 0.01% by weight to 50% by weight, particularly preferably 0.1% by weight to 30% by weight.

The stents comprising the compounds of the formula (I) are, where appropriate, additionally coated with a membrane. This membrane serves, for example and preferably, for controlling the release of medicinal substances and/or for protecting the active ingredient-containing stents from external influences.